

# Difference between the Inflammatory Reaction Caused by the Placement of a Conventional Laparoscopic Access and a Single Access (Single Port) in Pigs

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## ABSTRACT

Single access (SA) has been developed to replace conventional laparoscopy (CL) in order to reduce trauma. However, it is a controversial issue.

**Objectives:** To compare the acute inflammatory responses of CL and SA, considering only the trauma caused by the placement of the access port, at first time without pneumoperitoneum or other surgical manipulation. The variations of serum interleukin (IL)-4, -6, -8 and -10, tumor necrosis factor-alpha (TNF- $\alpha$ ) and C-reactive protein (CRP) were evaluated.

**Materials and methods:** Twenty pigs were randomly divided into two groups: a SA group and a CL group. In the SA group, the procedure began with a 2.5 cm skin incision, aponeurosis and peritoneum, and then the single-access device (Gelport<sup>®</sup>) was placed without pneumoperitoneum. In the CL group, the incision was performed on the skin, aponeurosis and peritoneum, and the four trocars were placed only with the traction of the abdominal wall. Once the access points were placed, blood samples were collected to measure the cytokines and CRP at: time zero (T0), immediately after anesthesia (including intubation); T1, immediately after the access point(s) was placed; T2, 120 minutes after the access point(s) was placed; and T3, 240 minutes after the access point(s) was placed.

**Results:** The concentrations of IL-4 and TNF- $\alpha$  decreased between T0 and T3. IL-10 and CRP also decreased, but not significantly. IL-6 and IL-8 increased, but not significantly.

**Conclusion:** During the study, there was no significant difference between the inflammatory response triggered exclusively by placing the SA and CL without pneumoperitoneum.

**Keywords:** Interleukin, Laparoscopy, Pig, Single port, Trauma.

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## INTRODUCTION

Advances in minimally invasive surgery, such as laparoscopy, have brought undoubted benefits to patients because they are less traumatic to the tissues. Recently, a technique was introduced that accesses the peritoneal cavity using a single access (SA) ('single port' or laparoscopic and endoscopic single site, LESS). It is different from conventional laparoscopy (CL), which regularly uses three or more access points. This new method aims to further reduce the morbidity of surgical procedures. However, the real benefits of SA in terms of tissue damage are controversial.<sup>1</sup> Furthermore, the procedures that use SA, such as nephrectomy and pyeloplasty, are technically more difficult to perform. Therefore, in patients undergoing CL procedures, the inflammatory effects need to be evaluated more carefully and compared with SA to evaluate the benefits of this new technique.

The degree of tissue damage caused by both open and laparoscopic surgery can be measured by the immune humoral response mediated by cytokines.<sup>1-4</sup> These include interleukins (ILs), interferons, colony-stimulating factors, tumor necrosis factor-alpha (TNF- $\alpha$ ) and growth factors. The level of C-reactive protein (CRP) is also used as a marker of tissue damage. Interleukins are a large group of cytokines produced by T lymphocytes and some phagocytes and tissue cells. They have many functions, especially the induction of proliferation and differentiation of other cells that express specific IL receptors.<sup>5,6</sup> Tumor necrosis factor-alpha activates macrophages and granulocytes, increases the adhesion of leukocytes to the endothelium and induces the synthesis of acute-phase proteins.<sup>7,8</sup> C-reactive protein is involved in the stress response to surgery, stimulating the phagocytosis by neutrophils and tissue macrophages.<sup>9</sup>

## OBJECTIVE

The present study aimed to compare the acute inflammatory responses of CL and SA, considering only the trauma caused by the placement of the access point, by measuring the serum levels of IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$  and CRP in surgeries performed in an animal model (pig).

## MATERIALS AND METHODS

The present study was conducted at the Vicky Safra Surgery, Teaching and Research Center (Centro de Ensino e Pesquisa em Cirurgia-CEPEC-Vicky Safra) in association with the medical research laboratory of the Division of Urology (LIM55), with the approval of the Medical Ethics Committee of the School of Medicine of the University of São Paulo (Faculdade de Medicina da Universidade de São Paulo-FMUSP). The study was conducted according to the Ethical precepts of the animal research facility of FMUSP.

Twenty Landrace pigs (domestic pig) from a specialized farm were used in the present study. The animals were fasted, sanitized and injected intramuscularly with 3 ml xylazine and 4 ml ketamine, associated with intramuscular injection of 3 ml (15 mg) midazolam as a pre-anesthetic medication. The anesthesia, which consisted of 5 to 10 ml of thiopental, was administered by puncturing the ear vein before intubation. After this procedure, the animals were intubated with a 6 mm endotracheal tube, and 10 ml of thiopental, 4 ml of fentanyl and 2 ml of pancuronium were administered. The ventilation rate was set to 12 breaths per minute with 100% oxygen ( $FiO_2$ ) and 1.5% isoflurane. Every 40 minutes, 10 ml thiopental, 4 ml fentanyl and 2 ml pancuronium were administered. An ear vein was punctured in the contralateral ear to collect blood samples.

### Surgical Procedure, Collection of Blood Samples from Pigs and Analysis of the Samples

Two groups of pigs, with 10 animals each, were randomly assigned to SA or CL. The anesthetized pigs had their abdomen washed with 2% chlorhexidine disinfectant followed by antiseptics with 0.5% chlorhexidine alcohol, and sterile drapes were placed. The Gelport® (Applied Medical, California, EUA) device was used in the SA group, and a device from Storz® (Karl Storz, Tuttlingen,

Germany), which consisted of two 10 mm trocars and two, 5 mm trocars, was used in the CL group.

In the SA group, the procedure began with a 2.5 cm incision in the skin, aponeurosis and peritoneum, followed by placement of a SA device (Gelport®) without pneumoperitoneum (Fig. 1). No other surgical manipulation was performed; we only collected blood samples from the ear of the pigs. In the CL group, the antiseptic preparation was the same. Skin, peritoneum and aponeurosis incision was performed, and the trocars were placed without insufflating the abdominal cavity, only with traction on the abdominal wall. In total, four access points (trocars) were placed: a 10 mm umbilical access, a 5 mm access in the xiphoid appendix, a 10 mm access in the iliac fossa and a 5 mm access in the hypochondrium (Fig. 2).

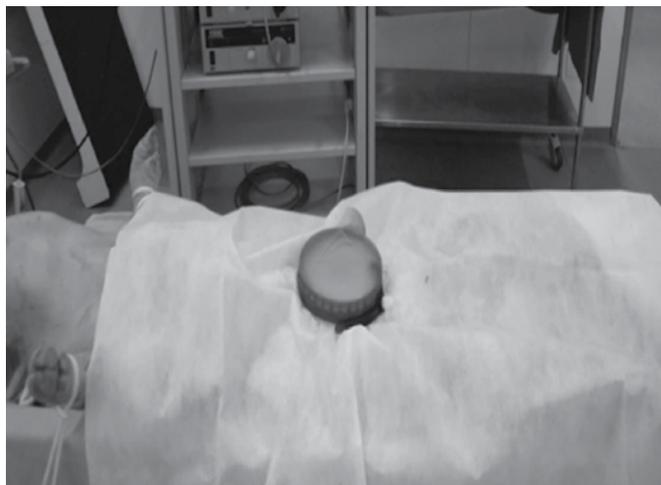
Once the access points were placed, blood was collected to measure the cytokines and CRP. Four samples were taken from each group: time zero (T0), immediately after anesthesia (including intubation); T1, immediately after the access was placed; T2, 120 minutes after the access was placed; and T3, 240 minutes after the access points were placed.

### Analysis of Blood Samples by ELISA

The blood samples were collected from the ear vein contralateral to the ear used for the anesthesia. The samples were centrifuged, and the serum was immediately used to perform enzyme-linked immunosorbent assays (ELISAs). Swine IL-10, IL-4, IL-8 and TNF- $\alpha$  ELISA kits (Invitrogen Corporation, CA, USA) and a swine CRP kit (Pig CRP ELISA kit, Genway, CA, USA) were used.

### STATISTICAL ANALYSIS

Student's t-test and the analysis of variance (ANOVA) were used to compare the data between groups. The differences were considered significant when  $p \leq 0.05$ .



**Fig. 1:** Single port approach employed in the study 199 × 100 mm (81 × 122 DPI)



**Fig. 2:** Four trocars laparoscopic conventional approach employed in the study 167 × 110 mm (123 × 123 DPI)

## RESULTS

IL-4 and TNF- $\alpha$  showed a significant, but borderline, reduction between T0 and T3. IL-10 and CRP also decreased, but not significantly. IL-6 and IL-8 increased, but not significantly (Table 1).

Table 2 shows that there were no significant differences between the two groups in IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$  or CRP at 240 minutes (T3). There was a difference in the IL-4 level between the two groups only at T1. TNF- $\alpha$  showed a difference between groups at T0. A possible explanation for this finding is that TNF- $\alpha$  increased due to trauma during the transportation of the animals, which were supposedly healthy and had no visible lesions when they reached the laboratory. This difference persisted through T1 (immediately after the trocars were placed) but disappeared in the following measurements.

**Table 1:** Changes in IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$  and CRP in all 20 pigs between T0 and T3 (240 minutes)

	Mean $\pm$ standard deviation (pg/mL)	P
T0: IL-4	0.184 $\pm$ 0.076	0.004*
T3: IL-4	0.123 $\pm$ 0.013	
T0: IL-6	0.253 $\pm$ 0.131	0.437
T3: IL-6	0.271 $\pm$ 0.173	
T0: IL-8	0.046 $\pm$ 0.005	0.228
T3: IL-8	0.054 $\pm$ 0.027	
T0: IL-10	0.116 $\pm$ 0.045	0.240
T3: IL-10	0.108 $\pm$ 0.038	
T0: TNF- $\alpha$	0.072 $\pm$ 0.007	0.018*
T3: TNF- $\alpha$	0.068 $\pm$ 0.004	
T0: CRP	3.112 $\pm$ 0.278	0.117
T3: CRP	3.011 $\pm$ 0.290	

\*Significant

**Table 2:** Comparisons of serum cytokine and CRP concentrations between the SA group and CL group at T0 (immediately after anesthesia), T1 (immediately after the trocars were placed), T2 (120 minutes after the trocars were placed) and T3 (240 minutes after the trocars were placed)

	IL-4 (pg/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	IL-10 (pg/ml)	TNF- $\alpha$ (pg/ml)	CRP (pg/ml)
T0						
SA group	0.151 $\pm$ 0.788	0.199 $\pm$ 0.121	0.044 $\pm$ 0.052	0.096 $\pm$ 0.022	0.068 $\pm$ 0.006	3.102 $\pm$ 0.242
CL group	0.218 $\pm$ 0.059	0.308 $\pm$ 0.122	0.047 $\pm$ 0.058	0.135 $\pm$ 0.055	0.077 $\pm$ 0.006	3.123 $\pm$ 0.324
p-value	0.46	0.5	0.277	0.052	0.006*	0.873
T1						
SA group	0.143 $\pm$ 0.041	0.254 $\pm$ 0.252	0.045 $\pm$ 0.058	0.135 $\pm$ 0.126	0.067 $\pm$ 0.005	3.057 $\pm$ 0.266
CL group	0.235 $\pm$ 0.072	0.228 $\pm$ 0.079	0.055 $\pm$ 0.017	0.174 $\pm$ 0.136	0.078 $\pm$ 0.005	2.993 $\pm$ 0.156
p-value	0.003*	0.76	0.101	0.526	0.001*	0.522
T2						
SA group	0.138 $\pm$ 0.031	0.190 $\pm$ 0.097	0.050 $\pm$ 0.006	0.105 $\pm$ 0.030	0.067 $\pm$ 0.004	2.947 $\pm$ 0.381
CL group	0.160 $\pm$ 0.032	0.306 $\pm$ 0.188	0.054 $\pm$ 0.015	0.122 $\pm$ 0.038	0.070 $\pm$ 0.005	2.938 $\pm$ 0.314
p-value	0.137	0.098	0.469	0.286	0.168	0.957
T3						
SA group	0.129 $\pm$ 0.012	0.227 $\pm$ 0.122	0.051 $\pm$ 0.018	0.098 $\pm$ 0.029	0.066 $\pm$ 0.002	3.058 $\pm$ 0.305
CL group	0.118 $\pm$ 0.012	0.314 $\pm$ 0.209	0.057 $\pm$ 0.035	0.119 $\pm$ 0.044	0.070 $\pm$ 0.006	2.963 $\pm$ 0.005
p-value	0.061	0.27	0.649	0.239	0.128	0.482

\*Significant; Concentrations are presented as means  $\pm$  standard deviation

## DISCUSSION

The goal of continually improving surgical techniques, with an emphasis on reducing tissue damage, has inspired several advancements in minimally invasive procedures. In this regard, video laparoscopic represents a major advance, as it is now the gold standard for the surgical treatment of many diseases. The main reason for using this technique is to minimize tissue damage, resulting in a weaker inflammatory response, which results in less pain, shorter postoperative recovery and earlier return to activities, in addition to better esthetic results. Techniques that, in theory, should cause less tissue trauma to the patients, such as natural orifice transluminal endoscopic surgery (NOTES) and SA or 'single port' or 'LESS,' have also been developed. However, it is still unclear whether these techniques, particularly the SA technique, are actually less traumatic than CL.<sup>10</sup>

The evaluation of the inflammatory response to surgical trauma can be performed by measuring the ILs in blood, and previous studies have emphasized the importance of IL-4, IL-6, IL-8 and IL-10.<sup>11</sup> Tumor necrosis factor-alpha and CRP are also used to evaluate the inflammatory response to surgical trauma.<sup>10-12</sup> However, many factors interfere with their measurement accuracy, and the results obtained with these markers are conflicting.<sup>10-13</sup>

The present study aimed to evaluate the acute inflammatory response triggered by the surgical trauma that results from two techniques currently used: SA, considered by some authors a less invasive procedure,<sup>10</sup> and video laparoscopic surgery. For this purpose, the serum levels of ILs, TNF- $\alpha$  and CRP were measured in a porcine model.

In most protocols, the SA technique is performed through a single 2.5 cm incision that passes through the skin, aponeurosis and muscles, called the port or access point. A trocar is placed on the access point, allowing instruments such as the optic and two to four clamps to be introduced into the body. This differs from laparoscopy, which is performed through a 1.0 cm incision in the abdominal wall, usually in the umbilical region, and two or three, 5 or 10 mm incisions in the abdominal wall, called ports or access points, where the trocars will be placed. Many video laparoscopic procedures use two 10 mm access points (one umbilical and one in the iliac fossa) and two 5 mm access points (one in the region of the xiphoid appendix and the other in the hypochondrium), so this setting was used for the present study. The SA technique imposes a space restriction between the hands of the surgeons when they manipulate surgical clamps, making the procedure considerably more difficult than CL. Therefore, the benefit to the patient depends on the experience of the surgeon.<sup>14</sup>

To evaluate only the inflammatory response triggered by the access points, pneumoperitoneum was not used because the gas used in SA or CL surgery may influence the inflammatory response markers (ILs, TNF- $\alpha$  and CRP).<sup>10-13</sup> Some studies have evaluated the differences between SA and video laparoscopy but included the entire surgical procedure.<sup>14</sup> However, each surgery may have different variables, such as the dissection length, bleeding and infections, which could modify the results. The present study evaluated only the trauma resulting from the access points. Recently, a study with a design similar to ours was published.<sup>15</sup> However, the author used pneumoperitoneum for 1 hour after the access points were placed, which could influence the IL levels.<sup>10-12</sup>

In the present study, we used healthy pigs as an animal model, all from a farm in a nearby town. The town is approximately 1 hour away from the lab, and the pigs were brought to the lab on the day of the procedure. This decision may have influenced the results because of the possibility that the transportation was traumatic for the animals. However, blood samples were collected from both groups at T0, immediately after anesthesia and intubation. Four pigs per day arrived on different days, and two pigs went to each group randomly, to minimize the influence of the temperature each day and variations in travel time. Ideally, the animals should be kept longer in the lab before the procedures, but this was not possible because of a municipal law that forbids maintaining these animals in the city. This was also the reason why the study time was set to 4 hours; ideally, the inflammatory response should be monitored for longer periods, such as days or weeks. Furthermore, ideal conditions,

such as housing, medications and assessments of other inflammation foci, e.g. lungs require larger technical and financial resources, in addition to imposing postoperative suffering on the animals.

Nakano et al (2007) observed increased IL-4, 3 hours after laparotomy in rats, confirming that the sampling time used in the present study was sufficient to evaluate IL-4.<sup>16</sup> In a study on IL-4 and IL-10, Shapenko et al considering that these markers have anti-inflammatory action in animals, demonstrated that they are suitable for studies in humans.<sup>17,18</sup> The reduction of IL-4 might have resulted from the minor trauma caused by the access points in the present study. In support of this hypothesis, the reduction observed in the SA group (0.151 to 0.129 = 0.022) was lower than the reduction observed in group 2 (0.218 to 0.118 = 0.100). This effect may warrant investigation in future studies. Kimura et al (2006), who studied the kinetics of IL-4, IL-6, IL-8 and IL-10, observed increases in all these markers except for IL-4.<sup>12</sup>

IL-6 has been used as a marker of response to surgical trauma by several authors.<sup>9-11</sup> Shenkin et al demonstrated variations in the IL-6 level 90 minutes after skin incision, reaching a peak level at 4 hours.<sup>19</sup> Cruickshank et al found increased IL-6 after 2 to 4 hours in several procedures, demonstrating a correlation between IL-6 and tissue trauma.<sup>20</sup>

A study by Hao et al (2012), which analyzed the inflammatory response promoted by LESS and by CL in a procedure for treating varicocele in children, did not observe significant differences between the two procedures regarding IL-6 or TNF- $\alpha$ .<sup>10</sup> Matsumoto et al (2005), who compared laparoscopic nephrectomy, hand-assisted laparoscopy (insertion of a hand into the abdomen through a minimal incision) and the open technique, measured the inflammatory response in pigs by analyzing peritoneal IL-6 and plasma TNF- $\alpha$ , showing that the laparoscopic technique had weaker inflammatory effects than hand-assisted or open surgery.<sup>1</sup> Ypsilantis et al (2012) conducted a study of IL-6, IL-8, TNF- $\alpha$  and CRP in 20 pigs, aiming to evaluate the inflammatory responses to LESS and CL. The pigs were divided into four groups: SA with pneumoperitoneum for 1 hour; CL with pneumoperitoneum; only pneumoperitoneum; and only anesthesia. The analysis of IL-6, IL-8, TNF- $\alpha$  and CRP did not show differences between the various procedures.<sup>14</sup> Wang et al (2009) compared open pyeloplasty with laparoscopic pyeloplasty in children, analyzing IL-6, IL-8, IL-10, TNF and CRP.<sup>21</sup> They found that, in both groups, IL-6 was higher after 4 hours, and IL-6 and CRP were higher in open surgery.

IL-8 has also been used in studies on the inflammatory response to surgical trauma.<sup>22</sup> This IL has the ability to

recruit neutrophils and monocytes to the inflammatory site.<sup>12,23</sup> A study published by Kato et al (1997) showed a significant increase of IL-8 from baseline to 4 hours after the procedure in the plasma of patients who underwent upper-abdominal surgery.<sup>22,24</sup> In contrast, Torres et al (2008) did not observe increased IL-8 at any time up to 48 hours after laparoscopic cholecystectomy with 'standard and low' pneumoperitoneum pressure.<sup>23</sup>

IL-10 is also used to measure the inflammatory response to surgical trauma. A study by Dimopoulou et al (2007) that correlated IL-10 with infectious complications showed that IL-6, IL-8 and IL-10 increased proportionally with the surgery time (2, 4, 6 and 8 hours).<sup>25</sup> In a study that measured IL-6, IL-8 and IL-10 to analyze the surgical stress response to laparoscopic and open techniques, no change in the levels of these cytokines after 4, 24 or 48 hours was observed.<sup>21</sup> An analysis of laparoscopic surgery using standard-or low-pressure pneumoperitoneum did not show changes in the levels of IL-8 and IL-10.<sup>24</sup>

Tumor necrosis factor-alpha has an important proinflammatory action. This cytokine initiates the production of adhesion molecules that lead to the activation and proliferation of neutrophils.<sup>1</sup> Matsumoto et al found high plasma TNF- $\alpha$  1 hour after surgery, reaching a peak at 4 hours and decreasing after 48 hours.<sup>1</sup> Wang et al did not observe significant changes in the level of TNF- $\alpha$  when comparing laparoscopic pyeloplasty with open pyeloplasty in children.<sup>21</sup> In the present study, TNF- $\alpha$  was significantly higher at T0 than at T3 when the 20 pigs were analyzed together. We think this increase was related to the transportation of the animals.

C-reactive protein is often used as a marker of surgical trauma because it has a predictable response to acute tissue damage. Its action is related to the activation of the complement cascade and the stimulation of phagocytes by neutrophils and macrophages. C-reactive protein increases by 4 hours after surgery and peaks at 24 hours.<sup>9</sup> C-reactive protein is lower in response to laparoscopic surgeries compared to open surgeries.<sup>9</sup>

Some authors analyze peritoneal and plasma interleukins to evaluate the traumatic effects of surgery.<sup>1</sup> In the present study, we chose to analyze only blood samples because we did not want to perform any manipulation inside the abdominal cavity. Because we chose not to use pneumoperitoneum, we only placed the access points and did not perform any further trauma.

The strengths of the present study include the fact that it is, to our knowledge, the only one that has compared the SA and CL techniques without handling structures inside the peritoneal cavity. It is also the only study comparing SA and CL without using pneumoperitoneum. The main limitation is that we had only 4 hours to collect the

samples. Although studies using ILs demonstrate that more time could provide more consistent results, the present study allowed as much time as some other studies.<sup>1</sup> The present study aimed to achieve a short-term analysis, excluding the risk of infections or other traumas. In this regard, the transportation of the animals from the farm to the lab was a variable that could not be controlled due to legal impediments.

Like other studies that used rats, dogs or pigs, the present study was conducted in a porcine animal model.<sup>1,16,26</sup> Greco et al compared SA and CL in humans, but a nephrectomy was performed in these patients, which might have influence the analysis of ILs because that surgery involves different aspects of dissection and surgical trauma.<sup>14</sup>

The present study showed that there was no difference between SA surgery and CL surgery in terms of inflammatory stress in the absence of induced pneumoperitoneum. To our knowledge, this is the first study using access ports exclusively, without pneumoperitoneum. SA imposes more technical difficulty on the surgeon and a consequent risk to patients. Therefore, CL surgery remains the most appropriate. However, it is still unclear whether the ILs were increased with both techniques because the two types of access cause a minor inflammatory reaction, and it is also not certain whether there are other, more accurate ways to assess the degree of surgical trauma. Future studies should be performed to validate our findings.

During the first 4 hours after the opening of access points, there was no significant difference between the inflammatory response triggered by the SA technique and the CL technique, without pneumoperitoneum, as assessed by the levels of IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$  and CRP.

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